Yeast Chassis Design for Dicarboxylic Acids Production.

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Saccharomyces cerevisiae is a widely used microorganism for industrial biotechnology that has great potential to replace traditional petrochemical synthesis. Optimization of cell factories for production of different biotechnological products is still a cost and time inefficient process. Availability of pre-optimized yeast chassis cells, with improved precursor supply, will overcome such hurdles. Building upon this premise, we have developed a framework for rational design of chassis strains combining genome-scale metabolic models with a multi-objective metaheuristic approach. Here, we present the non-intuitive gene deletion targets optimized for growth-product coupled production of a family of C4-dicarboxylic acids, namely fumaric, succinic and malic acids. Several multi-gene deletion strains, including the chassis cell and the final producer strains, were implemented and experimentally tested. The strains encompassing the chassis backbone produce higher yields of respective targeted compounds than those containing merely the intuitive gene deletion(s). Taking advantage of the growth-product coupled design, best producing strains have been improved by adaptive laboratory evolution. Finally, evolved strains were characterized by employing a systems biology multi-omics strategy. As a proof-of-concept, we have generated pre-optimized chassis yeast cells for enhanced production of C4-dicarboxylic acids, hence showing that modular design strategies may contribute to accelerate cell factory development.